REMARKS/ARGUMENTS

Reconsideration of the above-identified application is respectfully requested. The Applicant has developed a new medicament and a method of using the medicament for preserving and storing a heart awaiting transplantation. That the medicament performs its intended function, that of preserving a heart awaiting transplantation, is abundantly clear from the experiment disclosed in the specification at pages 10-14, and shown in the results set forth in FIGS. 2-7. These results show that ATP and CP concentrations were remarkably reduced during preservation with cyclosporin A after 18 hours of preservation. Accordingly, new Claims 11-14, directed to a medicament for preserving hearts awaiting transplantation, have been added. As will be discussed below, the cited prior art does not teach using this medicament or the results of using the claimed medicament.

Claim Rejection - 35 U.S.C. § 103

Claims 6-7 and 9-10 stand rejected under 35 U.S.C. § 103 as being unpatentable over Raymond, Jurado *et al.* and Massoudy *et al.* for reasons of record and set forth in the Office Action filed August 4, 2003.

Notably, the Examiner does not state which of the three cited references are the primary references, and therefore, one must assume they are combined in the manner set forth in the Office Action mailed August 4, 2003 in which the Raymond patent was considered the primary reference. As will be shown below, it is respectfully submitted that the Examiner has failed to establish a *prima facie* case of obviousness. It is submitted that the Examiner must, *inter alia*, show "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Thrift*, 63 USPQ.2d 2002, 2006 (Fed. Cir. 2002). The factual inquiry of whether to combine references must be thorough in searching and cannot be performed wily nilly through the use of hindsight. Thus, the reason for there being some teaching motivation or suggestion to select and combine portions of the references relied upon as evidence of obviousness in such manner as the claims. Furthermore, deficiencies in the cited references

cannot be remedied by general conclusions about what is "basic knowledge". *In re Sang Su Lee*, 61 USPQ.2d 1430 (Fed. Cir. 2002).

The patent to Raymond is directed to a preservation solution that includes an isotonic solution for perfusing and storing a heart at room temperature while waiting transplantation. The Raymond solution is different from the solution claimed. The Raymond preservation solution requires an amiloride-containing compound and a small amount of adenosine. Again, it must be reiterated that the teachings of Raymond, *i.e.*, using amiloride and adenosine does not prevent ATP loss, which is the subject of the claimed invention. The fact that Raymond teaches "a" solution comprising various active ingredients carrying an expedience is inconsequential as they provide an entirely different solution for an entirely different purpose.

There Is No Motivation Or Suggestion To Combine Jurado et al. With Raymond

The article to Jurado *et al.* discusses studies that affect the cardiac muscle after heart transplantation and has nothing whatsoever to do with the claimed. The Examiner has cited Jurado *et al.* as teaching the benefits residing in short term CsA exposure of hearts employed in transplantation at levels of five parts per million; as claimed. The CsA is used in a cremophor vehicle. As pointed out, the Applicant's claimed method and medicament are for use for preservation, not after transplantation. Furthermore, there is no indication of any long term positive effect of the use of cyclosporin A nor is there any teaching of the solution of the medicament claimed. The experiment shown in the animals treated in Jurado *et al.* were treated after transplantation and over a lengthy period of time, *e.g.* 50 days. The ischemic/reperfusion process induced considerable alteration to cardiac muscle tissue of controlled animals. These effects were observed some weeks after the transplantation and diminished 30 days after post-transplantation. There is no discussion whatsoever in Jurado *et al.* of using cyclosporin A for the preservation of a heart awaiting transplantation. Thus, there is no suggestion nor is there any motivation to combine the teachings of Jurado *et al.* with Raymond. In other words, one considering the teachings of the Raymond patent and those of Jurado *et al.* would have no

information on whether to remove the amiloride compound and/or the adenosine from the Raymond preservation solution and substitute cyclosporin A.

There Is No Suggestion Or Motivation To Combine Massoudy et al. With Raymond

A 15 minute interruption of blood flow and reperfusion which Massoudy *et al.* describe in their article, has little or no relationship to the claimed method for blocking apoptosis during preserving and storing a heart. The major alteration in the canine preserved heart at 18 hours is the appearance of apoptotic cells that indicate a programmed cell death and also the reason that permanent damage occurs in the myocardium. This kind of damage is not seen in the Massoudy *et al.* process. Actually, the inventors did not find apoptotic cells in the solutions used in the claimed method until after 12 hours of preservation. Irreversible damage occurs when apoptotic cells are detected at 18 hours. The unique finding is that cyclosporine A prevents apoptosis and therefore prolongs the preservation time for the heart.

Preventing apoptosis has nothing to do with the findings that Massoudy *et al.* mention at this stage with a nitric oxide-dependent mechanism impeded by endothelin. Massoudy *et al.* disclose a reperfusion solution in which cyclosporin A is present in an amount of only 0.8 μM per liter. The Massoudy *et al.* article does not teach use of Raymond's amiloride in any type of solution whatsoever in the claimed amount. Massoudy *et al.* deal with a completely different technical problem over the present application, which is to minimize the reperfusion entry following the ischemic event. The teachings of Massoudy *et al.* show that the level of venus NO recovers faster after the ischemic episode and remains stable if the heart is perfused with the isotonic solution comprising cyclosporin A. Massoudy *et al.* is silent about the effects on an isolated heart preserved in the isotonic solutions disclosed in Massoudy *et al.* Thus, departing from Raymond as the primary reference, there is no particular reason for which one skilled in the art would turn to Massoudy *et al.* because Massoudy does not suggest that the isotonic solution therein disclosed would be particularly suited for solutions for preserving and storing a heart awaiting transplantation.

It is, therefore, respectfully submitted that the claims, as amended, are not obvious over Raymond, Jurado *et al.* and Massoudy *et al.* Specifically, none of the three references teach adding cyclosporin A to any kind of solution whatsoever in the amount claimed; Raymond does not use a cyclosporin, Jurado *et al.* does not teach CsA in an isotonic solution and the treatment is after a heart has been transplanted. The cited references do not create a *prima facie* case of obviousness. It is, therefore, respectfully submitted that the cited prior art does not make obvious the process claimed in Claims 6-7 and 9-10 and the medicament of new Claims 11-14.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on January 13, 2005.

Janet F. Sherrill